IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 16-139-WCB
ALVOGEN MALTA OPERATIONS LTD.,	)	
Defendant.	)	

PLAINTIFFS' OPPOSITION TO ALVOGEN'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY UNDER 35 U.S.C. § 101

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I. Nature and Stage of Proceedings

Plaintiffs ("Pernix") sued Alvogen for infringement of patents that cover Pernix's Zohydro® ER.[1] Alvogen seeks to sell infringing generic copies of Zohydro® ER before the patents-in-suit expire. On March 16, 2018, Alvogen moved for summary judgment of invalidity under 35 U.S.C. § 101 (D.I. 112), and Pernix moved for summary judgment of no invalidity under § 101 (D.I. 114). Pernix submits this brief in opposition to Alvogen's motion.

II. Summary of Argument

The Court should deny Alvogen's motion for summary judgment because the claims of the patents-in-suit recite eligible subject matter under § 101.

First, the claims are not directed to natural phenomena but rather to a method of altering a natural condition (pain) by treating it with a non-naturally occurring oral dosage unit comprising an extended release formulation of a semi-synthetic opioid. Alvogen's theory that the claims recite ineligible subject matter because they "are premised on . . . the response of the human body to [a particular] formulation" (D.I. 112 at 8) would invalidate all method of treatment claims, contrary to the directive from the Supreme Court in *Mayo* and the Federal Circuit in *CellzDirect* that such claims remain patent-eligible.

Second, the claims do not recite a conventional method, as this Court already determined when it construed the claims and held that "the [claimed] method of treating pain in the hepatically impaired patient is **different than the prior art's method** of treating pain in that same patient." D.I. 69 at 3 n.2. Alvogen ignores the Court's *Markman* findings and the five prior art extended release opioids that required dosage adjustments for hepatically impaired

[1] Pernix dropped patents and claims to narrow the issues in the case, and currently asserts claims 1-4, 11-12, 17 and 19 of U.S. Patent Nos. 9,265,760 ("the '760 Patent"), and claim 1 of U.S. Patent No. 9,339,499 ("the '499 Patent") (collectively, the "asserted claims" of the "patents-in-suit."). The patents-in-suit share a common specification.

patients, which establish that the claims contain an inventive concept.

Third, Pernix's patents do not raise preemption concerns because the claims are confined to specific methods of treating pain using certain hydrocodone oral dosage units that produce a particular pharmacokinetic profile and do not require an adjustment in the starting dose when administered to patients with mild and moderate hepatic impairment relative to patients without hepatic impairment. It is undisputed that not all hydrocodone oral dosage units meet that requirement.

Fourth, at a minimum, disputed facts preclude granting summary judgment of invalidity under § 101.[2] Alvogen's motion turns on the interpretation of "numerous prior art references" that purportedly discuss the "the common practice of administering hydrocodone and other opioids for treating pain in patients with hepatic impairment." D.I. 112 at 5. Whether that "common practice" involved the **same** method claimed by the patents-in-suit (it did not) raises factual disputes.

III. Facts

Pain is the most common reason for doctor visits in the United States. Ex. A, '760 Patent col. 1:33-37. It can be acute, lasting until the underlying condition is healed or removed, or chronic, persisting for years. *Id.* Physicians prescribe Pernix's Zohydro® ER, an extended release ("ER") formulation containing hydrocodone (an opioid), to manage pain severe enough to require daily, around-the-clock, long-term treatment for which alternative treatment options are inadequate. *Id.* at 1:48. Hepatic impairment (*i.e.*, reduced liver function) complicates

[2] By contrast, the Court can grant Pernix's motion for summary judgment of **no** invalidity under § 101 (D.I. 114). Unlike Alvogen's motion, Pernix's motion relies not on disputed facts but rather on: (1) Supreme Court and Federal Circuit legal guidance that method of treatment claims recite patent-eligible subject matter; (2) admissions by Alvogen's expert that the claimed dosage units do not occur in nature; and (3) the Court's *Markman* findings that the claims recite unconventional steps.

treatment of pain because the liver metabolizes (breaks down) most opioids. So the same dose of an opioid generally leads to higher blood levels of drug (C_{max} and AUC) in hepatically impaired patients compared to patients without hepatic impairment, meaning that hepatically impaired patients receive too much drug (*i.e.*, an overdose). Such increases in AUC or C_{max} "can lead to many problems, including need for adjusting dose, complications for physicians in prescribing, need for liver function tests, lack of availability of correct doses, lack of availability of certain medications, to those with hepatic impairment," sedation, respiratory depression, or death. *Id.* at 2:44-47, 4:30-36.[3] Thus, physicians **decrease** the starting dose of opioids in patients with hepatic impairment to counter the effect of reduced liver function. *Id.* at 2:52-56.[4]

In fact, the patents-in-suit describe five prior art commercial ER opioid products that required a reduction in dose for hepatically impaired patients. *Id.* at 3:10-4:29. They also discuss the 2013 Bond Abstract regarding another **hydrocodone** ER formulation, later approved by the FDA as Vantrela™ ER. That product had a clinically significant difference in AUC for patients with moderate hepatic impairment: "the delivery of **[ER] hydrocodone** . . . led to **systemic exposure to hydrocodone** [AUC] **that was ~70% higher in subjects with moderate hepatic impairment vs normal hepatic function**." *Id.* at 2:56-65. This increase in AUC required a label instruction stating that patients with mild or moderate hepatic impairment should "[i]nitiate therapy with **one half of the recommended initial dose** and titrate carefully." Ex. B at 1. But lowering the dose complicates treatment. Unable to rely on the starting dose known to provide safe and effective pain relief in the unimpaired patient population, physicians instead

[3] C_{max} and AUC are PK parameters that measure how well and quickly the body breaks down a drug. C_{max} refers to the maximum concentration of drug in the patient's blood, and AUC (Area Under the Curve) is a measure of total exposure to the drug over time. *Id.* at 11:12-23.

[4] Unless otherwise indicated: "Ex." refers to an exhibit attached to the Declaration of Josh Calabro, Esq.; emphases have been added; and objections have been omitted.

must determine an appropriate dose for each hepatically impaired patient individually, while adjusting dosages and monitoring the patient to try to safely achieve efficacy on a case-by-case basis. *See* Ex. A at 4:30-36.

The inventors here unexpectedly found that physicians could prescribe the **same** starting dose of certain hydrocodone ER compositions in patients with and without hepatic impairment, thus providing a safer and simpler way of treating those patients. Ex. A at 4:40-65. That new method of administration minimizes the increase in AUC and C_{max} that one normally expects in hepatically impaired patients, rendering that increase "not clinically significant." *Id.* at 5:37-41, 23:27-38. The asserted claims, therefore, recite methods of treating pain in patients with mild or moderate hepatic impairment by administering an ER hydrocodone oral dosage unit, and require particular PK profiles and/or no starting dose adjustment for patients with mild and moderate hepatic impairment relative to patients without hepatic impairment.

IV. Argument

A. Legal Standard

1. Patent-Eligible Subject Matter

Section 101 provides that a patent may be obtained for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," excepting only laws of nature, natural phenomena, and abstract ideas from those broad categories of patent-eligible subject matter. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014), quoting *Ass'n for Molecular Pathol. v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013). To prevail on their defense under § 101, defendants must prove by clear and convincing evidence that: (1) the claims of the patents-in-suit are directed to a law of nature or a natural phenomenon, and, if so, (2) the additional elements of the claims lack an "inventive concept" that "transform[s] the nature of the claim into a patent-eligible application." *Mayo Collab. Servs.*

v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1296-97 (2012); *Alice*, 134 S. Ct. at 2355; *Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1342 (Fed. Cir. 2013) ("[A]ny attack on an issued patent based on a challenge to the eligibility of the subject matter must be proven by clear and convincing evidence."), *cert. granted, judgment vacated*, 134 S. Ct. 2870 (2014); *Berkheimer v. HP Inc.*, 2017-1437, 2018 U.S. App. LEXIS 3040 at *15 (Fed. Cir. Feb. 8, 2018) ("Any fact . . . that is pertinent to the invalidity conclusion [under § 101] must be proven by clear and convincing evidence.")

The Supreme Court has cautioned that courts must "tread carefully in construing [the subject matter eligibility] exclusionary principle lest it swallow all of patent law" because "[a]t some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" *Alice*, 134 S. Ct. at 2354, quoting *Mayo*, 132 S. Ct. at 1293-94. Thus, "a process is not unpatentable simply because it contains a law of nature," and "an application of a law of nature . . . to a known structure or process may well be deserving of patent protection." *Mayo*, 132 S. Ct. at 1293-94 (citation omitted). "The 'directed to' inquiry [*i.e.*, *Alice* step one], therefore, cannot simply ask whether the claims **involve** a patent-ineligible concept, because essentially every routinely patent-eligible claim involving physical products and actions **involves** a law of nature and/or natural phenomenon." *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1335 (Fed. Cir. 2016) (emphasis original). Rather, the Court should consider "whether the claims . . . focus on a specific means or method . . . or are instead directed to a result or effect that itself is the [ineligible concept] and merely invoke generic processes . . . ." *McRO, Inc. v. Bandai Namco Games Am., Inc.*, 837 F.3d 1299, 1314 (Fed. Cir. 2016). *Alice* step two requires analysis of the claims as a whole, considering their "elements both individually and as an ordered combination," to determine whether they "recite well-

understood, routine, conventional activity already engaged in by the scientific community." *Rapid Lit. Mgt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1047 (Fed. Cir. 2016) (citation omitted); *accord Exergen Corp. v. KAZ USA, Inc.*, Case Nos. 2016-2315, 2016-2341, slip op. at 7-12 (Fed. Cir. Mar. 8, 2018) (non-precedential) (attached as Ex. C).

2. Summary Judgment

"The patent eligibility inquiry may contain underlying issues of fact," *e.g.*, "whether a claim element or combination of elements is well-understood, routine, and conventional to a skilled artisan in the relevant field." *Berkheimer*, 2018 U.S. App. LEXIS 3040, at *8, *15. Summary judgment is appropriate only in the absence of any genuine issue of material fact, where the evidence establishes that the moving party is entitled to a judgment as a matter of law. Fed. R. Civ. P. 56(a); *Celotex Corp. v. Catrett*, 477 U.S. 317, 330 (1986). A factual dispute is "genuine" if a reasonable fact-finder could return a verdict for the non-movant and "material" if it would affect the outcome of the case. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248-49 (1986). In deciding a summary judgment motion, the Court must view the evidence in a light most favorable to the party opposing the motion, and must draw all reasonable inferences and resolve all doubts in the favor of the non-moving party. *Id.* at 255.

B. The patents-in-suit are not directed to natural phenomena under step one of *Alice*.

1. Method of treatment claims are patent-eligible.

The asserted claims are not directed to an ineligible concept under step one of *Alice* because they recite methods of treating pain. The Supreme Court, the Federal Circuit, and the USPTO have uniformly acknowledged that method of treatment claims are patent-eligible. First, the Supreme Court expressly limited its holding in *Mayo* by clarifying that the claims it invalidated under § 101 were "[u]nlike [] a typical patent on a new drug or a **new way of using**

an existing drug," which remain patent-eligible. *Mayo*, 132 S. Ct. at 1302.[5] The claims in *Mayo* recited a method of "**optimizing** therapeutic efficacy," not a method of **treating** a disease. *Id.* at 1295. The claimed methods involved measuring metabolites in the bloodstream to help calibrate the appropriate dosage of thiopurine drugs. Those claims "amounted to nothing more than observing or identifying the ineligible concept" (*CellzDirect*, 827 F.3d at 1048) because they did not require anyone to do anything with the data obtained via the claimed steps, apart from merely recognizing the law of nature itself (*i.e.*, "the relationship[] between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm"). *Mayo*, 132 S. Ct. at 1296.

> [T]he court construed the claim[s] . . . as not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable. . . [A] doctor using Mayo's test [thus] could violate the patent even if he did not actually alter his treatment decision in the light of the test. . . . [The claims] tell a treating doctor to measure metabolite levels and to consider the resulting measurements in light of the statistical relationships they describe. In doing so, they **tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations**.

Id. at 1296, 1302. Second, the Federal Circuit held in *Rapid Lit. Mgt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1049 (Fed. Cir. 2016), that "describing [a] process [as] the natural ability of the subject matter to undergo the process does not make the claim 'directed to' that natural ability." Otherwise, Courts "would find patent-ineligible methods of . . . treating cancer with

[5] A panel of the Federal Circuit voiced unanimous agreement with this interpretation of *Mayo* at a recent oral argument. *Vanda Pharms. Inc. v. West-Ward Pharms.*, No. 2016-2707 (Fed. Cir. argued Dec. 5, 2017) (Judge Lourie (4:00-5:00): "The Supreme Court has, in effect, blessed [method of treatment] claim[s] in *Mayo*, so what's the problem under 101?"; Judge Hughes (7:40-8:15): "[W]e have dozens of cases where we've held dosing patents eligible . . . **where the drug is known**, the side effects are known, and they come up with **new methods of treatment or dosages** . . . ."; Judge Prost (9:23-9:41): "[The claim in *Mayo*] didn't have any specificity as to what the method of treatment was . . . It didn't go to the dosing."), *available at*: http://www.cafc.uscourts.gov/oral-argument-recordings/search/audio.html?title=vanda&field_case_number_value=&field_date_value2%5Bvalue%5D%5Bdate%5D=

chemotherapy (as directed to cancer cells' inability to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin)," which would contravene well-settled law. *Id.* Third, on May 5, 2016, the USPTO published patent eligibility guidance that analyzed the following fact pattern and hypothetical claims:

> Applicant has discovered that the presence of a protein known as "JUL-1" in a person's body is indicative that the person has julitis. . . . Prior to applicant's invention, and at the time the application was filed, julitis was conventionally treated with anti-tumor necrosis factor (TNF) antibodies. . . .
>
> 2. A method of diagnosing julitis in a patient, said method comprising:
> a. obtaining a plasma sample from a human patient;
> b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody; and
> c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected. . . .
> 7. A method of treating a patient with julitis, the method comprising administering an effective amount of anti-TNF antibodies to a patient suffering from julitis.

Ex. D at 9-11. The USPTO found claim 2 ineligible because it recites "a mere data gathering step necessary to use the ['naturally occurring'] correlation." *Id.* at 11-12. By contrast, the USPTO found claim 7 patent-eligible because "[a]lthough the claim recites a nature-based product limitation (the anti-TNF antibodies), analysis of the claim as a whole indicates that the claim is focused on a process of practically applying the product to treat a particular disease (julitis), and not on the product *per se*." *Id.* at 15-16. The USPTO did not need to proceed to *Alice* step two, *i.e.*, the conventional nature of claim 7's method made no difference for purposes of § 101 because the claim was not directed to an ineligible concept. *Id.* Finally, following *CellzDirect*, on July 14, 2016, the USPTO issued another memorandum on patent eligibility. The USPTO found that *CellzDirect* accords with USPTO practice because it reaffirms the eligibility of claims that "focus[] on a process for achieving [a] desired outcome . . . like

thousands of other claims that recite . . . methods of treating disease." Ex. E at 2, citing *CellzDirect*, 827 F.3d at 1048-49.

Alvogen mischaracterizes Pernix's claims as directed to "no more than an observation," *i.e.*, the "discovery of the human body's metabolism of [ER hydrocodone] formulation[s]." D.I. 112 at 2; *see id*. at 11 ("Evaluating the human body's physiological response to a pharmaceutical formulation is a quintessential patent-ineligible law of nature."). Alvogen spends considerable pages attempting to distill the claims to this singular "basic concept." D.I. 112 at 1, 3, 6-7, 12. Alvogen, however, ignores the language of the claims, which recite a method of treatment—not an "observation" or "evaluat[ion]." The inventors did observe an unexpected physiological response to a particular dosage unit as one step along their path towards the claimed inventions. But "that is not where they stopped, nor is it what they patented." *CellzDirect*, 827 F.3d at 1048. Rather, "as the first party with knowledge of" that response, they were "in an excellent position to claim applications of that knowledge." *Id.*, quoting *Myriad*, 133 S.Ct. at 2120 (quoting *Association for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part)). And "[t]hat is precisely what they did. They employed their . . . discovery to create a new and improved way" of **treating pain** in patients with hepatic impairment. *Id.* ("The end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to . . . a '*method of producing* a desired preparation of multi-cryopreserved hepatocytes.'") (citation omitted) (emphasis original).

As the foregoing case law and PTO guidance make clear, the focus must remain on the language of the claims, as different claims that "embody, use, reflect, rest upon, or apply" the same natural law can nevertheless lead to divergent conclusions under step one of *Alice*. *Mayo*,

132 S. Ct. at 1293. The claims here include the dispositive element that the Supreme Court found absent from the claims in *Mayo*, namely, the application of that discovery by claiming a new way to dose hydrocodone ER products to patients with hepatic impairment. *See Molecular Pathology*, 689 F.3d at 1349 (Bryson, J., concurring in part and dissenting in part) ("[T]he discovery of [naturally-occurring gene] sequences is an unprotectable fact, just like Dr. King's discovery of the chromosomal location of the BRCA1 gene. Of course, Myriad is ***free to patent applications of its discovery***."), *rev'd in part on other grounds*, *Myriad*, 133 S. Ct. at 2120. The asserted claims do not leave the treatment decision unresolved by merely requiring a doctor to "consider" a naturally-occurring correlation; the claims expressly require a "subsequent treatment decision," *i.e.*, no adjustment in the starting dose for patients with mild and moderate hepatic impairment relative to patients without hepatic impairment.[6] *Mayo*, 132 S. Ct. at 1302.

Endo lends no support to Alvogen's argument because there the patentee "concede[d] the first step of the *Mayo* analysis." *Endo Pharms., Inc. v. Actavis Inc.*, 2015 U.S. Dist. LEXIS 127104, at *15 (D. Del. Sept. 23, 2015); *Endo Pharms., Inc. v. Actavis Inc.*, 2015 U.S. Dist. LEXIS 155034, at *3, *7 (D. Del. Nov. 17, 2015) (patentee "admitted" that the claims are directed to a natural law.) And the claims in *Endo*, like those in *Mayo*, left the treatment decision unresolved, instructing physicians to "measur[e] a creatinine clearance" and then administer an unspecified "lower dosage," "in dependence on which creatinine clearance rate is found." 2015 U.S. Dist. LEXIS 127104, at *3-4. Those claims thus amounted to "informing the patient or prescribing physician that the bioavailability of oxymorphone is increased in patients with renal impairment." 2015 U.S. Dist. LEXIS 155034, at *7; 2015 U.S. Dist. LEXIS 127104,

[6] Claims 1-4 and 11 of the '760 patent explicitly recite that "the starting dose is not adjusted relative to a patient without hepatic impairment," while the remaining asserted claims require a PK profile that enables such dosing.

at *15; *see Mayo*, 132 S.Ct. at 1298 (the claims "simply tell doctors to gather data from which they may draw an inference in light of the correlations," *i.e.*, "the claims inform a relevant audience about certain laws of nature"). The asserted claims, by contrast, do not merely "inform" an audience of a natural law. Rather, they recite administering—which the Court construed to require "delivering into the body"—a specific dose of an ER hydrocodone oral dosage unit to treat pain.[7]

2. The claims require administering a non-naturally occurring oral dosage unit.

The asserted claims are directed to the administration of non-naturally-existing compositions, which independently renders the claims eligible under the first step of *Alice*. In *Molecular Pathology*, the Federal Circuit concluded that "claims to 'comparing' or 'analyzing' two gene sequences"—which occur in nature—"fall outside the scope of § 101 because they claim only abstract mental processes." *Id.* at 1334, *rev'd in part on other grounds*, *Myriad*, 133 S. Ct. at 2120. Yet the Court reached a different result for other claims even though they similarly recited an "abstract mental step of looking at two numbers and 'comparing' two host cells' growth rates." *Id.* at 1336. The Court held those claims eligible because, unlike the gene sequences, the host cells do ***not*** exist in nature but instead "arose from human effort":

> Claim 20 thus recites a screening method premised on the use of "transformed" host cells. Those cells . . . are not naturally occurring. Rather, they are derived by altering a cell to include a foreign gene, resulting in a man-made, transformed cell . . . . The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible. The fact that the claim also includes the steps of determining the cells' growth rates and comparing growth rates does not change the fact that the claim is based on a man-made, non-naturally occurring transformed cell — patent-eligible subject matter.

[7] The claims' recitation of a relative rather than absolute dosage makes no difference; requiring no adjustment in the starting dose sets a treatment decision to the same extent as requiring, *e.g.*, a 20 mg dose.

Id. at 1336-37. Notably, the inclusion of man-made cells alone rendered the claimed process patent-eligible, irrespective of whether the steps of that process were known in the art. *Id.* at 1337 ("Whether such processes, including claim 20, meet other tests for patentability, such as novelty or nonobviousness, is not before us.").[8]

The invention here uses hydrocodone, which is a semi-synthetic opioid, in the context of an oral dosage form, and neither the hydrocodone nor the dosage form exists in nature. Alvogen's expert Dr. Weinberger repeatedly admitted that at his deposition:

> Q. And this oral dosage form of hydrocodone doesn't appear in nature, right?
> A. That is my understanding, sir. That is correct.
> Q. It's not a natural phenomenon, right?
> A. I believe you are correct. . . .
> Q. Okay. And extended release formulations of hydrocodone do not appear in nature, right?
> A. I believe that is correct.
> Q. And they're not a natural phenomenon, right?
> A. That is correct. . . .
> Q. Okay. And the particular dose of hydrocodone extended-release tablet to use is not something that would appear in nature, right?
> A. These tablets do not appear in nature, no. . . .

Ex. F at 10:25-11:12, 12:4-13, 13:7-12, 25:7-26:5 (objections omitted). Thus, the claims are not directed to a natural phenomenon because they require administering a man-made dosage unit that contains a non-naturally-occurring opioid.

C. The claims recite an inventive concept under step two of *Alice*.

Even if the patents-in-suit claim a natural phenomenon (which they do not), they are still directed to patent-eligible subject matter because the claims recite an inventive concept. Alvogen repeatedly asserts that the patents-in-suit disclose "identical" formulations to those in the prior art. Alvogen's argument tracks verbatim the argument in its motion for summary judgment of invalidity by anticipation. *Compare* D.I. 112 at 1 *with* D.I. 119 at 3. As an initial

[8] *Endo* did not and could not overturn this Federal Circuit law. *See* Section IV(B)(1), *supra*.

matter, Alvogen improperly conflates subject matter eligibility and novelty. *Diamond v. Diehr*, 450 U.S. 175, 188-90 (1981) ("The 'novelty' of any element or steps in a process, or even of the process itself, is of **no relevance** in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter"; "whether a[n] invention is novel is **wholly apart** from whether the invention falls into [the § 101] categor[ies].").[9]

Regardless, Alvogen's argument fails because the claims recite unconventional **methods of using** ER hydrocodone compositions. And cases on which Alvogen relies confirm that such claims are patent-eligible. *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005) ("New uses of old products or processes are indeed patentable subject matter."), citing 35 U.S.C. § 101; *see* D.I. 119, at 13-15 (discussing *Perricone*). In *Mayo*, the Court interpreted the claims as "tell[ing] doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field," and found such "[p]urely conventional or obvious" activity "[in]sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 132 S. Ct. at 1298. By contrast, the claims here recite unconventional steps, namely, administering an ER hydrocodone oral dosage unit to patients with mild and moderate hepatic impairment without adjusting the starting dose relative to patients without hepatic impairment (or a PK profile that enables such dosing). Commercial prior art ER opioids required dosage adjustments for hepatically impaired patients. *See* Section III, *supra*. Thus, unlike the claims in *Mayo*, the claims here do not merely "append[]

[9] Alvogen also tries to disparage the invention by speculating about the purported lack of difficulty in developing it. D.I. 114 at 1-2. "But patent-eligibility does not turn on ease of execution or obviousness of application." *CellzDirect*, 827 F.3d at 1052 ("LTC's argument seems to be that, once it was discovered that hepatocytes could survive multiple freeze-thaw cycles, it would have been a simple task to repeat the known freeze-thaw process to arrive at the claimed invention. . . . Those are questions that are examined under separate provisions of the Patent Act.").

conventional steps" (*id.* at 1300) to a law of nature. Indeed, Alvogen admits that the wherein clauses requiring particular PK profiles and no starting dose adjustment for patients with mild and moderate hepatic impairment recite unconventional steps. D.I. 112 at 2 ("**Other than the wherein clauses**, the Asserted Claims merely recite the conventional and well-known method of treating pain.").

The Court's *Markman* decision forecloses any argument to the contrary. In its *Markman* decision, this Court rejected Alvogen's argument that the starting dose term does not limit the claims, and found that a physician would "not normally" give an hepatic impaired patient the same dose as an unimpaired patient, *i.e.*, such dosing was unconventional:

> [not] adjusting the starting dose relative to a patient without hepatic impairment is, in fact, a **manipulative difference over the prior art** . . . .
>
> the ability of a patient with a hepatic impairment to gain the same benefits from the opioid that a non-hepatically impaired patient receives in just one dose **differs from the prior art**. . . .
>
> the claim phrase explaining that hepatically and non-hepatically impaired patients get the same starting dose . . . does have an effect on how the administering step is performed . . . because patients with hepatic impairment ingest a **different dose than they normally would, given the prior art**;
>
> [s]ince the method of treating pain in the hepatically impaired patient is **different than the prior art's method** of treating pain in that same patient, having a patient ingest the same initial dose regardless of their hepatic impairment is not just a mental step.

D.I. 69 at 3 n.2. The Court's *Markman* findings therefore establish that the claims recite unconventional steps and satisfy step two of *Alice*. *See CellzDirect*, 827 F.3d at 1051 ("Repeating a step that the art taught should be performed only once can hardly be considered routine or conventional. This is true even though it was the inventor's discovery of something natural that led them to do so."). And those fact findings are not open for re-litigation. *Bondyopadhyay v. United States*, No. 14-147C, 2018 U.S. Claims LEXIS 79, at *14-15 (Fed. Cl.

Feb. 9, 2018) ("[P]rior findings and the claim construction based on those findings are law of the case and 'are not available for redetermination'"), *quoting Del Mar Avionics, Inc. v. Quinton Instrument Co.*, 836 F.2d 1320, 1324 (Fed. Cir. 1986).

Finally, Alvogen cites one prior art reference, Jain, for its alleged disclosure that "the bioavailability of an ER version of Vicodin® in patients afflicted with HI was known to be similar in patients with and without mild or moderate HI." D.I. 112 at 5. As an initial matter, there never has been a commercial ER version of Vicodin®. Gudin Decl. Ex. A ¶ 139; *see Berkheimer*, 2018 U.S. App. LEXIS 3040 at *18 ("The mere fact that something is disclosed in a piece of prior art . . . does not mean that it was well-understood, routine, and conventional."). Moreover, there is no data in Jain to support the conclusion that the bioavailability was "similar." Indeed, Jain provides eighteen data figures and seventeen data tables regarding Jain's ER Vicodin formulation ("Vicodin® CR"), but conspicuously absent is any hepatic impairment data. Gudin Decl. Ex. A ¶ 143. And, Jain's Vicodin® CR formulation is a combination product (hydrocodone and acetaminophen)—Jain neither teaches nor provides any reasonable expectation that one could administer a **single entity** ER hydrocodone dosage unit to patients with mild and moderate hepatic impairment without adjusting the starting dose relative to unimpaired patients, as required by the asserted claims. Gudin Decl. Ex. A ¶¶ 139-77. The Examiner expressly recognized as much when addressing Jain in the reasons for allowance of the '760 patent claims. *See* D.I. 69 at 3 n.2 (acknowledging the unpredictability of the art). At most, Alvogen has raised a disputed fact that precludes summary judgment in its favor, especially in view of the five single-entity ER opioids discussed in the specification that required dosage adjustments. *See* Section III, *supra*; *Berkheimer*, 2018 U.S. App. LEXIS 3040 at *19-23

("[O]n this record summary judgment was improper, given the fact questions created by the specification's disclosure" of "purportedly unconventional" activities).

D. The claims do not raise preemption concerns.

Finally, Alvogen contends that "*any* single-ingredient hydrocodone ER oral formulation that meets the limitations in the wherein clauses are preempted by the claims." D.I. 112 at 15 (emphasis original). Alvogen's argument—anything that meets the limitations is preempted by the claims—would apply to (and invalidate) every patent. Section 101 bars claims that preempt **use of a natural law**; "preempting" a formulation makes no sense. The only "natural law" that Alvogen identifies is the "natural law providing the similar bioavailability of hydrocodone-only ER oral dosage forms in patients with and without mild and moderate" hepatic impairment. *Id.* But no such law exists. The single-entity ER hydrocodone oral dosage unit disclosed in the Bond abstract, for example, does not meet the claimed PK profile and requires an adjusted starting dose for patients with mild and moderate hepatic impairment.[10] The asserted claims thus do not preempt all uses of hydrocodone, all uses of hydrocodone oral dosage units, all uses of ER hydrocodone oral dosage units, all uses of single-entity ER hydrocodone oral dosage units, all uses of single-entity ER hydrocodone oral dosage units to treat pain, or even all uses of single-entity ER hydrocodone oral dosage units to treat pain in patients with mild or moderate hepatic impairment.

V. Conclusion

For the foregoing reasons, the Court should deny Alvogen's motion.

[10] The Bond formulation was approved in 2017 as Vantrela™ ER, and the Vantrela™ ER label states: "In patients with mild or moderate hepatic impairment, **initiate therapy with one half of the recommended initial dose** followed by careful dose titration. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg." Ex. B at 1.

Respectfully submitted,

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